UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/130,887	08/07/1998	BRUCE G. GOLD	899-50283	6989

7590 05/06/2002

KLARQUIST SPARKMAN CAMPBELL
LEIGH & WHINSTON
ONE WORLD TRADE CENTER SUITE 1600
121 SW SALMON STREET
PORTLAND, OR 972042988

EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	21

DATE MAILED: 05/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/130,887	Gold
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- Th MAILING DATE of this communication app ars on th cover sh t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 1-24-02

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 6, 7, 9-11, 15-17, and 19-21 is/are pending in the applica

4a) Of the above, claim(s) 19 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 6, 7, 9-11, 15-17, 20, and 21 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 6, 7, 9-11, 15-17, and 19-21 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. The amendment filed 1-24-02 has been entered and fully considered.

2. Claims 8, 12, 14 and 18 are canceled. Claims 6-7, 9-11, 15-17 and 19-21 are pending.

3. Restriction is as set forth in Paper No. 15, mailed 12-15-00.

4. Applicant's election with traverse of Group III, claims 6-18 and 20 in Paper No. 15 is acknowledged. The traversal is on the ground(s) that the limitation "selecting (one) or more FK506 analogs comprises selecting one or more analogs that do not substantially inhibit FKBP-12 rotamase activity when administered to a patient at dosage levels up to about 100 mg/kg body weight/day," as recited in claim 19, is not a further method step but rather an inherent pharmacological characteristic of the selected FK-506 analog.

This argument has been fully considered but is not persuasive. The examiner understands applicants arguments to assert that FK-506 analogs inherently do not substantially inhibit FKBP-12 rotamase activity when administered to a patient at dosage levels up to about 100 mg/kg body weight/day. However, the examiner finds no such evidence of record to support this assertion. In contrast, it appears that the parent claims are directed to FK506 analogs which differentially bind FKBP-12 and differentially affect rotamase activity. Thus, it is presumed that the FK506 analogs of the invention differentially affect rotamase activity. Such effects may not necessarily be based upon the analogs individual FKBP-12 binding characteristics. Accordingly, it appears that the limitation serves to recite an additional step which is required for the selection of particular analogs (i.e., administration to patients), including evaluation of rotamase activity in

patients which is not inclusive of binding. As the step is not encompassed by the parent claim, it is not further limiting, constitutes a new method and presents additional search burden to the examiner.

The requirement is still deemed proper and is therefore made FINAL.

5. Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

Claim Objections

6. Claim 11, is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 11 recites the method of claim 6 wherein the FK506 analog does not inhibit rotamase activity. The method does not appear to be further limited by the recitation as there is no step that results in the selection or identification of such compounds based on rotamase activity. (It is noted that rotamase is mis-spelled.) If applicants wish to limit the FK506 analogs or claim a method which results in the identification of such FK506 analogs then they should either note that the screening is of FK506 analogs that do not inhibit FKBP-12 rotamase activity, or include a selection step where compounds are selected based on such activity.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes at p. 11, compounds of Armistead et al., Acta Cryst., D51:522-528, 1995 which are FK506 analogs noted to exhibit Kd values between 1 and 100 nM. However, the claims recite FK506 analogs of the Armistead variety which exhibit Kd values of greater than 10 uM. Thus, the instant disclosure fails to describe even a single member of the compounds which fall under the claimed characteristics and which exhibit a Kd of greater than 10 uM. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art

to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

Yet in the instant case no written description is provided for even a single member of the claimed genus which in particular is identifiable using the claimed methodology, and therefore the written description provided by the specification does not meet the requirements of 35 USC 112, first paragraph.

9. Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

As set forth above, the specification describes at p. 11, FK506 compounds of Armistead et al., Acta Cryst., D51:522-528, 1995 which are noted to exhibit Kd values between 1 and 100 nM. However, the claims recite FK506 analogs of the Armistead variety which exhibit Kd values of greater than 10 uM. Neither the specification nor art recognizes such compounds exhibiting the recited affinities for FKBP-12. While the art of record clearly teaches FK506 compounds of alternative structure which exhibit such affinities and promote neurite outgrowth, the artisan is not readily apprised of any member as claimed which would more likely than not exhibit Kd values greater than 10uM and exhibit neurite outgrowth activity. As such is required for the claims, i.e., the identification of the relevant analogs, the method as claimed bears no reasonable expectation of success because the artisan lacks the guidance required to arrive at the claimed FK506 analogs. Thus the artisan would be required to conduct further experimentation to make and test any multitude of analogs within the FK506 backbone of Armistead to arrive at a compound which was experimentally shown to exhibit the required Kd value of greater than 10 uM and the ability to promote neurite outgrowth. Such experimentation is unpredictable in the art as each substituent would be expected to produce different affinities for FKBP-12 (as exemplified in Armistead) and could similarly exhibit different abilities to stimulate neurite outgrowth. There is no disclosed member as claimed which exhibits the required functions, is capable of selection, or identification as disclosed.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 6-7, 9-11, and 15-17 and 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims newly recite "selecting a FK506 analog that does not bind FKBP-12 wherein the compound that does not bind FKBP-12 is a compound that has an apparent K_d for FKBP-12 of greater than 10 μM." The FK506 analogs and second selection step are indefinite because they are defined by contradictory statements. The artisan cannot discern or select those analogs which do not bind and which also bind with a particular dissociation constant as the requirements are contradictory to each other. Further it is noted as to claims 20 and 21 that as disclosed in the specification at p. 11 and Armistead et al., Acta. Cryst. D51:522-28, 1995 none of the noted FK506 analogs of claim 21 are noted to possess Kd values of greater than 10 uM. In contrast all of the values are in the range of 1-100 nM. Thus, the claims are indefinite to the artisan as it is unclear what the selection is for and what criteria must be met.

12. Claims 16-17 are indefinite as they depend from canceled base claim 14.

Claim Rejections - 35 USC § 102 or 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

14. Claims 6-7, 9, 11, and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Steiner et al., US Patent No. 5,801,197, Sept. 1, 1998, filed May 13, 1996.

Steiner et al., teach FK506 analogs characterized by their ability to bind (or not bind) FKBP12, inhibit rotamase activity and stimulate neurite outgrowth in DRG cultures, see in particular column 7, lines 1-6 and Tables I-IV. Thus, the reference teachings anticipate the claimed methods as the method steps are performed in the analysis and identification of the compounds of the '197 patent.

Applicants argue that the '197 patent teaches the selection of a compound that binds FKBP-12 with high affinity and that such selection does not teach or render obvious compounds that do not bind FKBP-12.

Applicants arguments filed 1-24-02 have been fully considered but are not persuasive. Applicants claims are indefinite with respect to the non-binding or binding characteristics of the FK506 analogs being screened and their selection. In particular the claims are directed to FKBP-

12 non-binding and binding compounds with dissociation constants greater than 10, and 30 μM. It is noted that while Steiner et al., teach a parallel between the potencies in FKBP-12 binding, the stimulation of neurite outgrowth and inhibition of rotamase activity, see in particular column 7, lines 1-5 and 15-36, there are no set limits to the binding constants for FKBP-12 or for inhibition of rotamase activity and there is no compound which exhibits such activity which is noted to be deficient in the stimulation of neurite outgrowth. Thus the range of Steiner is inclusive to the extent of compounds having dissociation constants of greater than 10 and 30 μM. It is clear from Steiner that binding is associated with rotamase inhibition and neuronal outgrowth. Based on the Ki test as disclosed at column 9, line 60-column 12, line 44 and Tables I and IV in particular, it is clear that the Ki values for the various compounds establish their ability to both bind FKBP-12, inhibit rotamase activity and promoting axonal outgrowth. It is noted that compound 7 exhibits a Kd of 80 uM and is effective at promoting neurite outgrowth with an 50% effective dose of greater than 10,000 nM in DRG cultures as disclosed in Table III. Thus, the reference teachings anticipate the claimed invention.

15. Claims 6-7, 9, 11, 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Armistead et al., US Patent No. 5,717,092, Feb. 10, 1998, filed Mar. 29, 1996.

Armistead et al., teach evaluation of candidate agents for the properties of FKBP12 binding, inhibition of rotamase activity and the ability to stimulate neurite outgrowth, see in particular column 15, lines 25-31, 49-67, and Examples 9-11. Thus, the reference teachings

anticipate the claimed methods as the method steps are performed in the analysis and identification of the compounds of the '092 patent.

Applicants similarly argue that Armistead '092 patent teaches the selection of a compound that binds FKBP-12 with high affinity and that such selection does not teach or render obvious compounds that do not bind FKBP-12.

Applicants arguments filed 1-24-02 have been fully considered but are not persuasive. Applicants claims are indefinite with respect to the non-binding or binding characteristics of the FK506 analogs being screened and their selection. In particular the claims are directed to FKBP-12 non-binding and binding compounds with dissociation constants greater than 10, and 30 μM. It is noted that while Armistead et al., teach a parallel between the potencies in FKBP-12 binding, the stimulation of neurite outgrowth and inhibition of rotamase activity, see in particular column 15, lines 26-31 and 49-67, there are no set limits to the binding constants for FKBP-12 or for inhibition of rotamase activity. Thus the range of Armistead is inclusive to the extent of compounds having dissociation constants of greater than 10, and 30 μM. It is clear from Armistead that binding is associated with rotamase inhibition and neuronal outgrowth. Based on the FKBP-12 binding test as disclosed at column 44, line 55-column 45, line 56 and the Table of compounds in column 45, in particular, it is clear that the Ki values for the various compounds establish their ability to both bind FKBP-12, inhibit rotamase activity, promote axonal outgrowth and are within the range of greater than 10,000, 30,000 and 50,000 nM as disclosed in the Table

at column 45. These ranges represent values within the range of those claimed of K_d greater than 10 and 30 μM. Thus, the reference teachings anticipate the claimed invention.

16. Claims 6-7, 9-11 and 15-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Steiner et al., Nature Medicine 3(4):421-28, April 1997.

Steiner et al., teach evaluation of FK506 analogs by the properties of FKBP12 binding, inhibition of rotamase activity and the ability to stimulate neurite outgrowth, see in particular abstract, figure legend of Table 1, p. 422, column 2 through p. 423, column 1, p. 424, column 2, lines 3 through p. 425, column 1, line 10 and Table 4. Thus, the reference teachings anticipate the claimed methods as the method steps have been performed in the analysis of the FK506 analog compounds of Steiner et al.

Applicants similarly argue that the Steiner teachings are of FKBP-12 binding compounds and not of compounds which do not bind FKBP-12 as claimed.

Applicants arguments filed 1-24-02 have bee fully considered but are not persuasive. Again it is noted that applicants claims are indefinite as they recite non-binding FKBP-12 compounds which bind with a particular affinity, a contradictory statement. In particular, it is noted that the Steiner reference notes the binding affinity for FKBP-12 as IC 50 as determined in Table 1. As this assay differs from that of Harding, Siekierka and Armistead, 5,654,332, as noted at p. 17, lines 9-17 of the specification, the Examiner is unable to compare the relative Kd values for the compounds disclosed. As the reference teaches the desired relationship, that is the association of FKBP-12 binding and the promotion of neurite outgrowth the properties of the Kd

values for which the reference is silent are believed to be inherently the same as that of the claims. It is applicant's burden to show unobvious distinction based on Kd as the Patent Office does not have sufficient research facilities to determine the values of the Steiner compounds. Thus, the reference teachings inherently meet the claim limitations absent factual evidence to the contrary.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 10 and 17 are rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by Steiner et al., US Patent No. 5,801,197, Sept. 1, 1998, filed May 13, 1996 (102(e)), Armistead et al., US Patent No. 5,717,092, Feb. 10, 1998, filed Mar. 29, 1996 (102(e)) and Steiner et al.,

Nature Medicine 3(4):421-28, April 1997 102(a), or, in the alternative, under 35 USC 103(a) as obvious over Steiner et al., US Patent No. 5,801,197, Sept. 1, 1998, filed May 13, 1996, Armistead et al., US Patent No. 5,717,092, Feb. 10, 1998, filed Mar. 29, 1996 and Steiner et al., Nature Medicine 3(4):421-28, April 1997.

Steiner et al., 1998, and Armistead et al., are as set forth above and teach claim 6.

Steiner et al., 1997 is as set forth above and teach the method of claim 6 with the exception of the Kd values for the subject FK506 analogs, although the values are presumed to be inherent absent factual evidence to the contrary.

Thus, Neither Steiner et al., 1998, Armistead et al., nor Steiner et al., 1997 teach the limitations of claims 10 and 17 wherein the FK506 analogs have Kd dissociation constants for FKBP-12 of greater than 100 uM and which are effective to promote neurite outgrowth. However, it is noted that Steiner 1998, Armistead, and Steiner 1997 teach the association of FKBP-12 binding, the stimulation of neurite outgrowth and inhibition of rotamase activity. Further, none of the references teach an upper limit to the range of FKBP-12 dissociation constants which are effective to promote neurite outgrowth potential, and thus the ranges as taught by the references do not appear to be exempt from any molecules which are recognized to exhibit binding to FKBP-12 at a Kd value of greater than 100 uM. Nonetheless, the limitation is only implicitly implied but not expressly taught by the references. Specifically, it is noted that Steiner 1998 teaches a FK506 analog (compound 7) with a Kd of 80 uM for FKBP-12 which is noted to be effective in promoting neurite outgrowth at an 50% effective dose of 10,000 nM, see

in particular Table I and Table III. Armistead also teaches a compound of the invention which exhibits a Kd value of 50 uM as disclosed at the Table of column 45. As set forth above Steiner 1997 is silent to the Kd as determined in the other references and thus the Kd values are unknown to the Examiner and artisan. While the disclosure seems to be equivalent to the claims, and the values of 50 and 80 appear sufficiently close to 100 to either anticipate or render the claims obvious, the Examiner can not definitively show that such references teachings of FK506 analogs selected with Kd values of 50 and 80 uM either anticipate or render obvious FK506 analog compounds with a Kd of greater than 100 uM, because the references fail to disclose the relative Kd values standard deviation and/or standard error for the disclosed values. Thus the Examiner and the artisan would be unable to immediately discern whether the respective molecules claimed are inherently the same, anticipated or obvious in view of Steiner et al., 1998, Armistead et al., or Steiner et al., 1997. Since the record does not allow the determination of patentability in this regard and the Office does not have sufficient facts or resources to determine the relationship of the molecules relative Kd values and similarity to each other, the burden shifts to applicants to provide evidence that the prior art disclosures would neither anticipate nor render obvious the claimed invention.

Status of Claims

20. No claims are allowed.

21. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
April 23, 2002

Gary L. Kunz

GARY L. KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600